

Figure S1

Figure S1. cNK and ILC subsets vary in expression of classical NK markers within blood, lymphoid, and mucosal tissues, Related to Figure 1

A. Plots depict gating strategy used to identify cNK and ILC subsets in blood, lymphoid, and mucosal sites of an individual donor. Frequencies (percent) of Live CD45+Lin- subsets delineated as CD56+CD127- cNK (blue), CD56+CD127+ ILC (red), and CD56-CD127+ ILC (black) are shown in each tissue. B. Live CD45+ lineage-negative (Lin1-: CD3, CD5 ; Lin2-: FcERI, CD11c, CD11b, CD14, CD19) CD56+CD127- cNK cells were further delineated by expression of CD94 and CD16. C. Histograms show CD16 expression by cNK (blue), CD56-ILC (black, shaded), and CD56+ (red) ILC subsets in each tissue. D. Representative plots depict frequencies (percent) of Live CD45+CD16-CD3-CD5- (Lin1-) populations within each tissue. Live CD45+ Lin1- cells further delineated by their expression of E. CD56 and F. CD127 into cNK and ILC subsets, respectively.

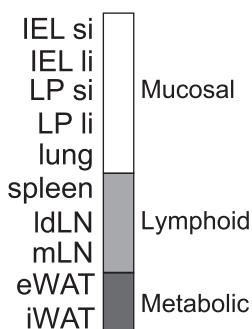
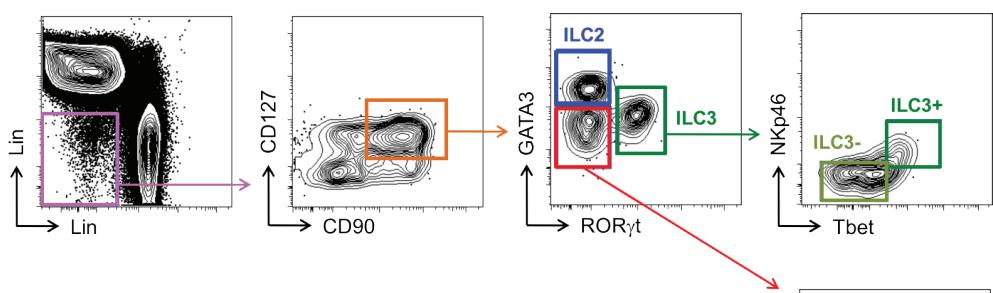
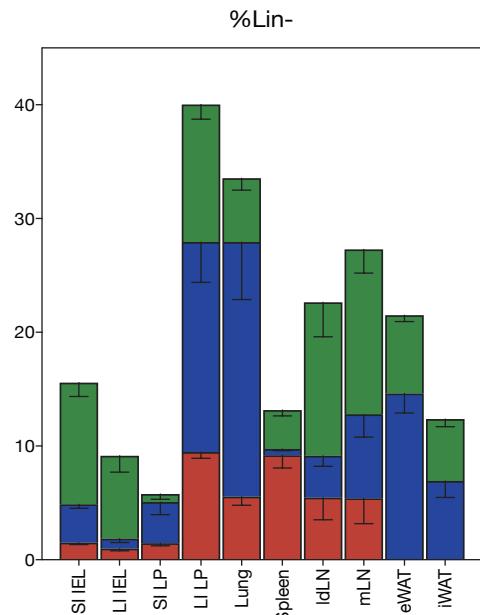
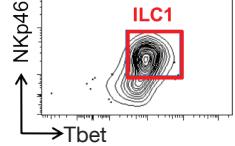
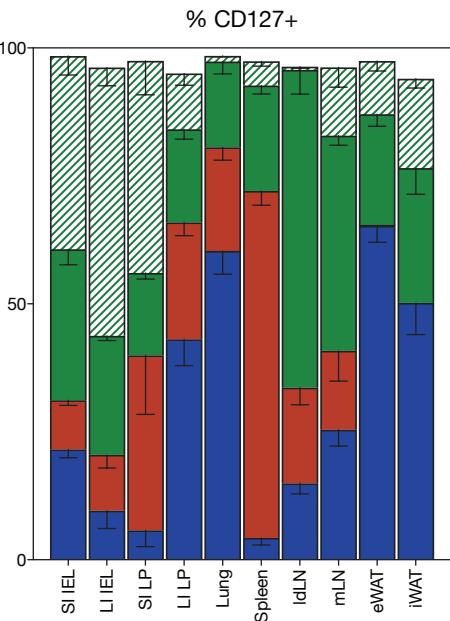
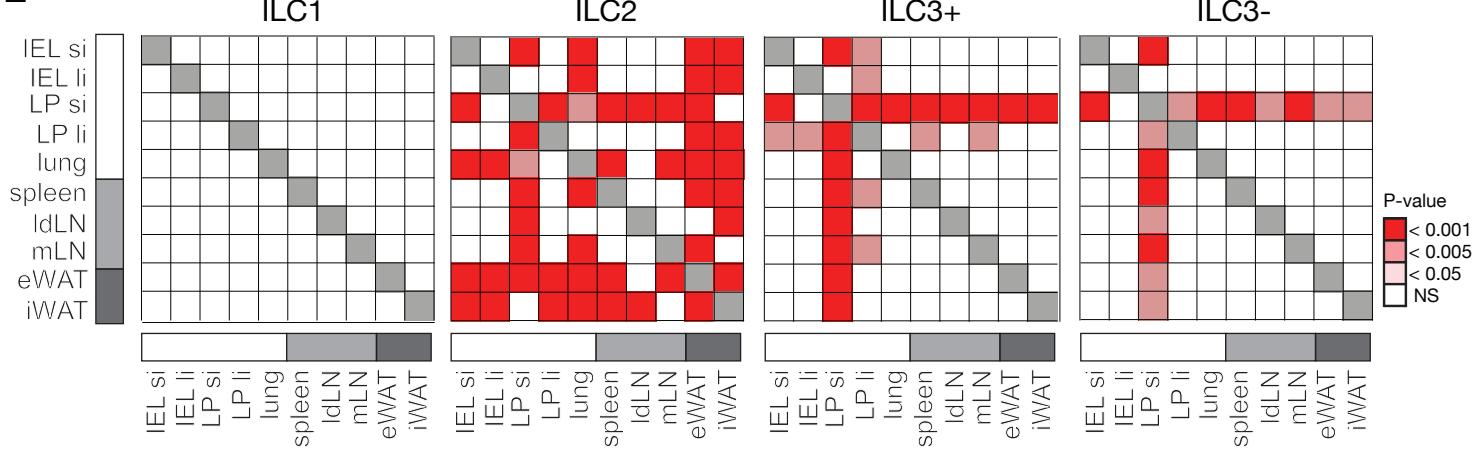
A**B****C****D****E****Figure S2**

Figure S2. Murine ILC compartmentalization is subset- and tissue-dependent, Related to Figure 2

A. Analysis overview depicts 8 murine tissues, from which 4 ILC populations were isolated, that sampled metabolic (eWAT, epididymal white adipose tissue; iWAT, inguinal white adipose tissue), lymphoid (mLN, mesenteric lymph node; IdLN, lung-draining lymph node), and mucosal sites. B. Schematic of gating strategy used to identify murine ILCs; lineage-negative (Lin^- ; CD3, CD5, FcERI, CD11b, CD11c, B220) CD90 $+$ CD127 $+$ ILC subsets were delineated into GATA3 $+$ ILC2, ROR γ T $+$ ILC3 and T-bet $+$ ILC1, which were further subdivided by their expression of NKp46 into NKp46 $+$ (ILC1 $+$, ILC3 $+$) or NKp46 $-$ (ILC1 $-$, ILC3 $-$) populations. C. Mean frequency (+SEM) of ILC1 (red), ILC2 (blue) and ILC3 (green) subsets expressed as a percent of total CD45 $+$ Lin^- is shown for each tissue and compiled from 11 mice. D. Mean frequency (+SEM) of total CD45 $+$ Lin^- CD127 $+$ NKp46 $+$ (solid) and NKp46 $-$ (striped) ILC subsets is shown within each tissue, and compiled from 11 mice. E. Distribution variance between ILC1 and ILC3 subset frequencies was assessed for each tissue by two-way ANOVA and adjusted for multiple comparisons using Holm-Sidak correction. Significant frequency variances between tissue pairs are indicated by p values, with red- and pink-shaded boxes depicting significant differences ($p < 0.001$, red; $p < 0.005$, light red; $p < 0.05$, pink; NS, not significant) and white boxes depicting no significant variance in subset frequency between anatomic sites. Data compiled from Lung (n=11), LdLN (n=8), IWAT (n=7), EWAT (n=7), MLN (n=7), Spleen (n=4), LI LP (n=3), LI IEL (n=4), and SI IEL (n=7) of 11 mice. See also Table S6 for a summary of samples and tissues used per figure panel.

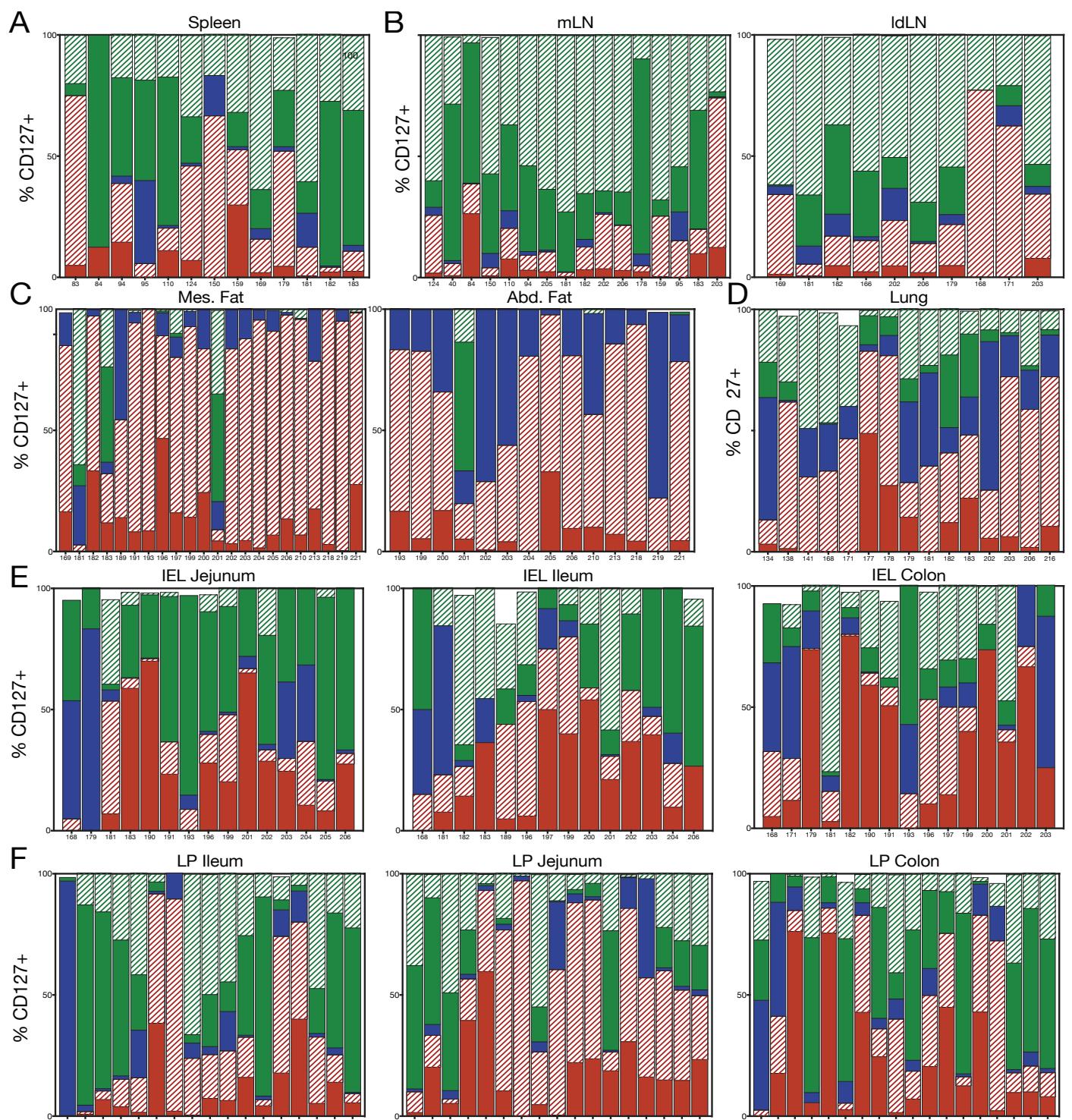


Figure S3

Figure S3. Tissue distribution and heterogeneous transcription factor expression among anatomically diverse ILC and cNK, Related to Figure 2

Mean frequency (+SEM) of total CD45+Lin-CD127+NKp46+ (solid) and NKp46- (striped) ILC subsets and ILC2 (blue) is shown by individual in A. spleen, B. lymphoid, C. metabolic, D. lung, E. mucosal intraepithelial, and F. mucosal lamina propria tissues. Data compiled from Abd. Fat (n=11), IEL Colon (n=15), IEL Ileum (n=14), IEL Jejunum (n=16), IdLN (n=10), LP Colon (n=18), LP Ileum (n=17), LP Jejunum (n=17), Lung (n=15), Mes. Fat (n=19), mLN (n=16), and Spleen (n=13) of 44 individuals. Representative flow cytometry histograms depict expression of G. TBET and H. EOMES by intestinal, lymphoid, and adipose ILC subsets from an individual donor. For donor information and all individual values shown see Table S1 and Table S2. See also Table S6 for a summary of donors and tissues used per figure panel.

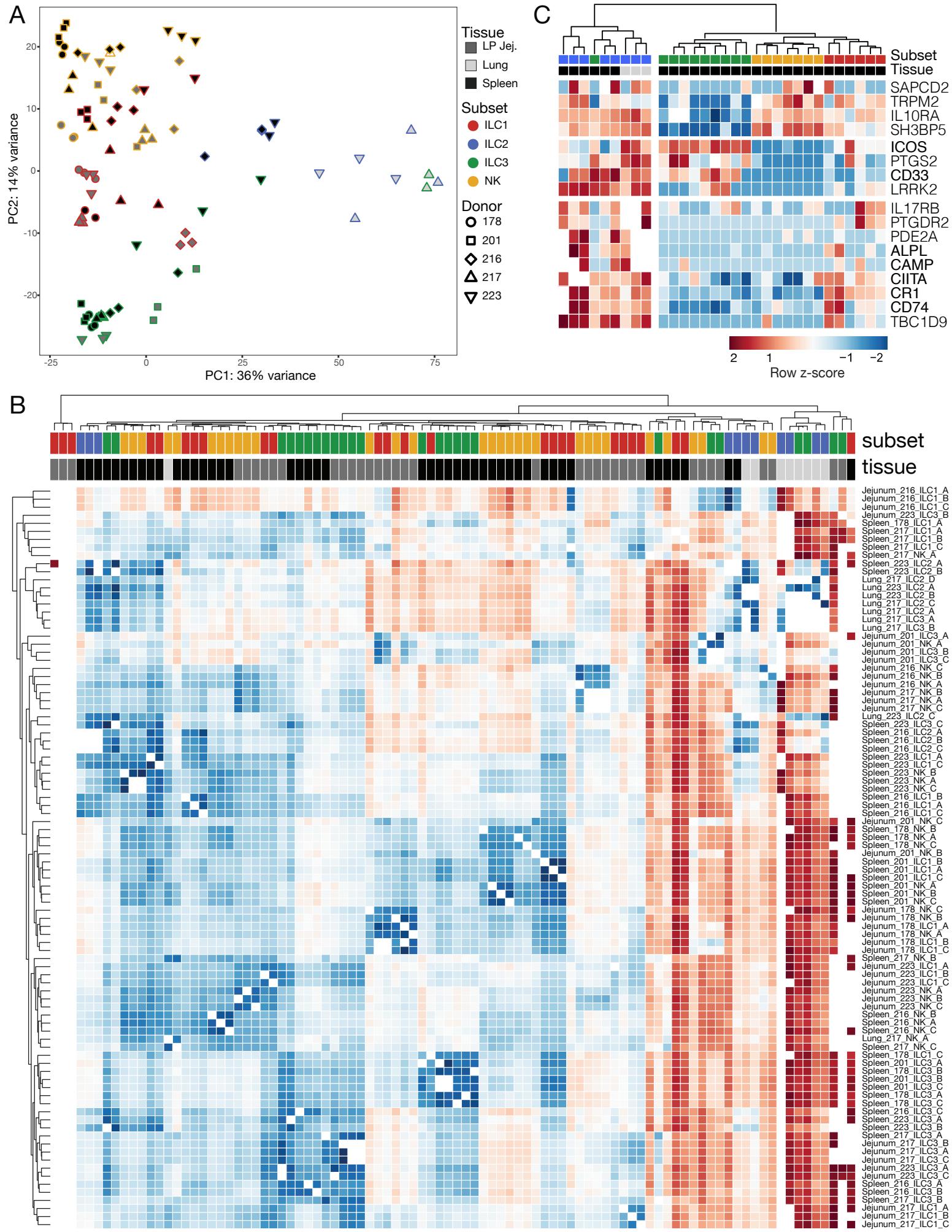
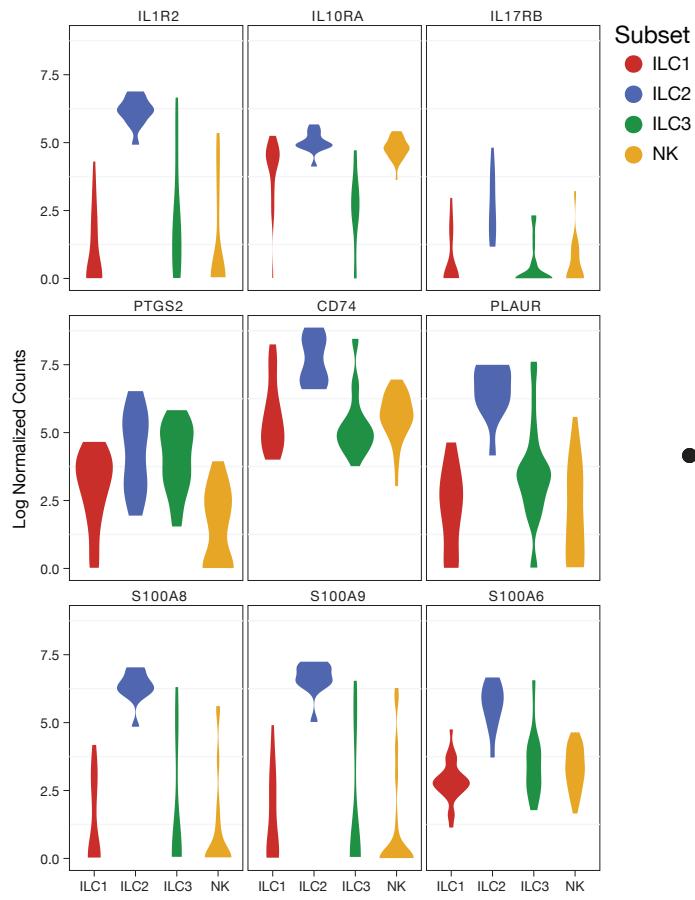


Figure S4

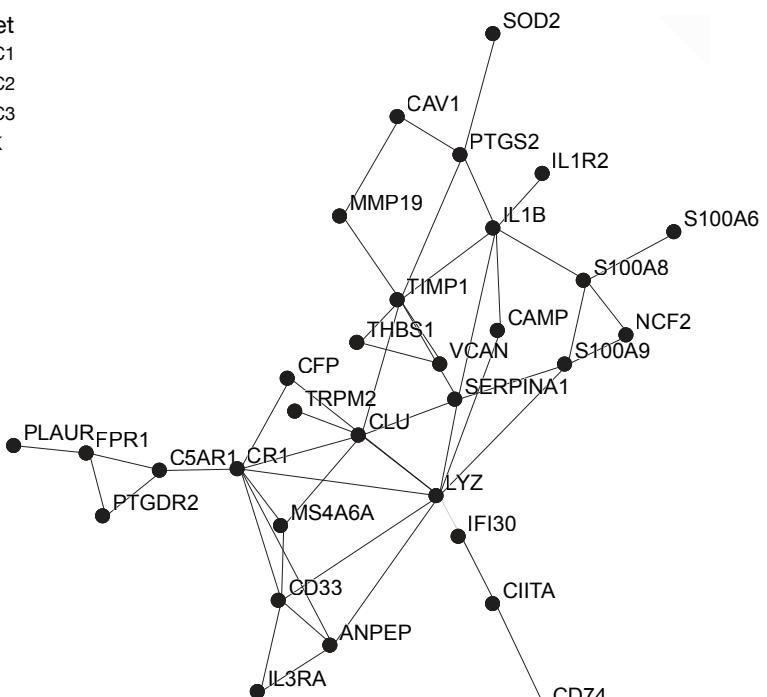
Figure S4. Extended donor and sample clustering analyses, Related to Figure 4

Transcriptional sequencing of mucosal and lymphoid ILCs from jejunum, lung and spleen of 5 individuals was performed by RNAseq. A. Principal component (PC) analysis of resultant transcriptomes shows stronger clustering among cNK (yellow), ILC1 (red), ILC2 (blue) and ILC3 (green) subsets than within jejunum (gray), lung (white), and spleen (black) tissues or individual donors. B. Heat map depicts unsupervised clustering of sample distances. Relative Euclidean distances between samples are indicated by row z-score, ranging from small (blue) to large (red). C. Unsupervised hierarchical clustering depicts transcriptional distinctions among ILC2s within mucosal versus lymphoid tissues. Shown here are significant ($q<0.1$, $p<0.001$) differentially expressed genes by subsets from the lung and/or jejunum. Relative gene expression is indicated by row z-score, ranging from -2 (low, blue) to 2 (high, red). Data compiled from LP Jejunum ($n=5$), Lung ($n=5$), and Spleen ($n=5$) of 5 individuals. See also Table S1 for donor information, and Table S6 for a summary of donors and tissues used per figure panel.

A



C



B

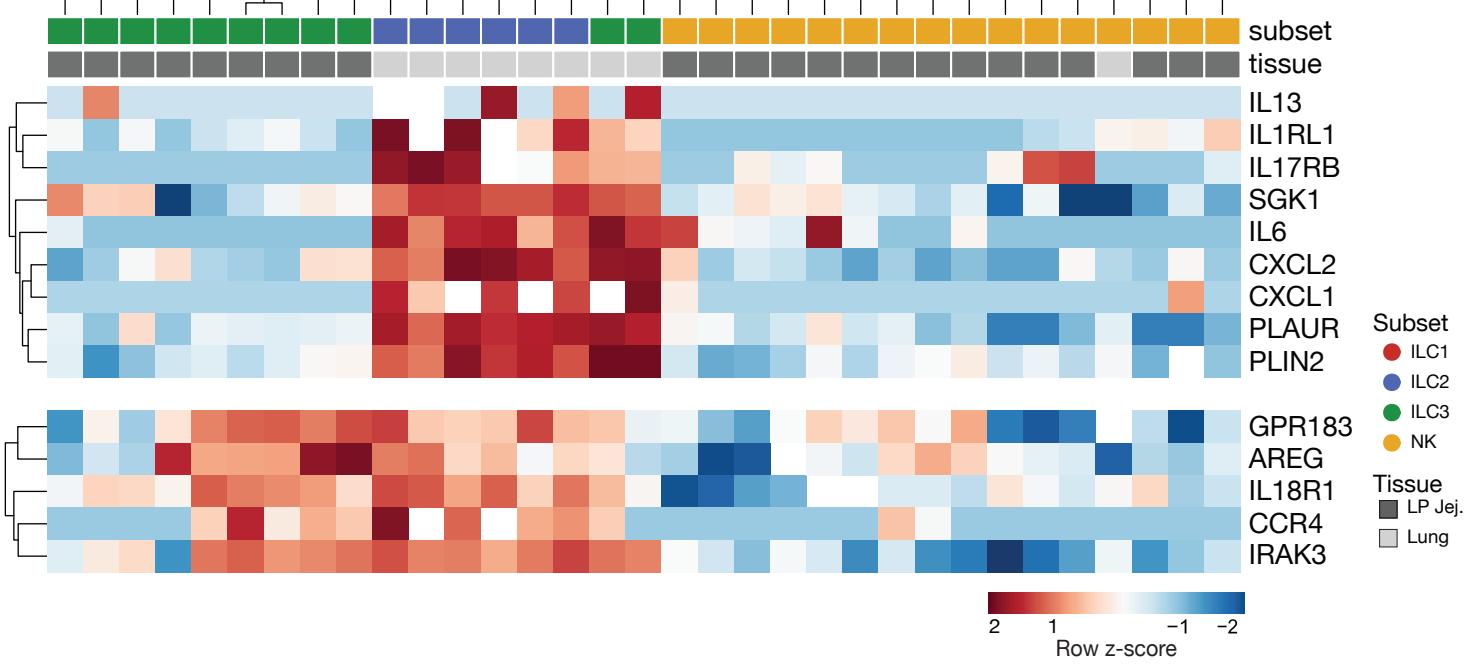


Figure S5

Figure S5. Extended analyses of ILC2 tissue- and subset-specific transcriptional signatures, Related to Figure 4

Transcriptional sequencing of ILC subsets from 5 individuals was performed by RNAseq. A. Violin plots of mean log normalized counts across all tissues show expression distribution of select subset-specific genes by cNK (yellow), ILC1 (red), ILC2 (blue) and ILC3 (green) across all tissues. B. Unsupervised hierarchical clustering depicts transcriptional distinctions among ILC subsets. Shown here are significant ($q<0.1$, $p<0.001$) differentially expressed genes enriched in ILC2 compared to ILC3 or cNK from the lung (white) and jejunum (gray). Relative gene expression is indicated by row z-score, ranging from -2 (low, blue) to 2 (high, red). C. Genes enriched in ILC2 subsets function in multiple pathways that are associated with type 2 immune responses. Known corresponding protein-protein interactions (STRING 10.0) are depicted by edges (solid line) connecting the nodes (genes). Data compiled from Jejunum (n=5), Lung (n=5), and Spleen (n=5) of 5 individuals. See also Table S1 for donor information, and Table S6 for a summary of donors and tissues used per figure panel.

A

Spleen



B

Jejunum

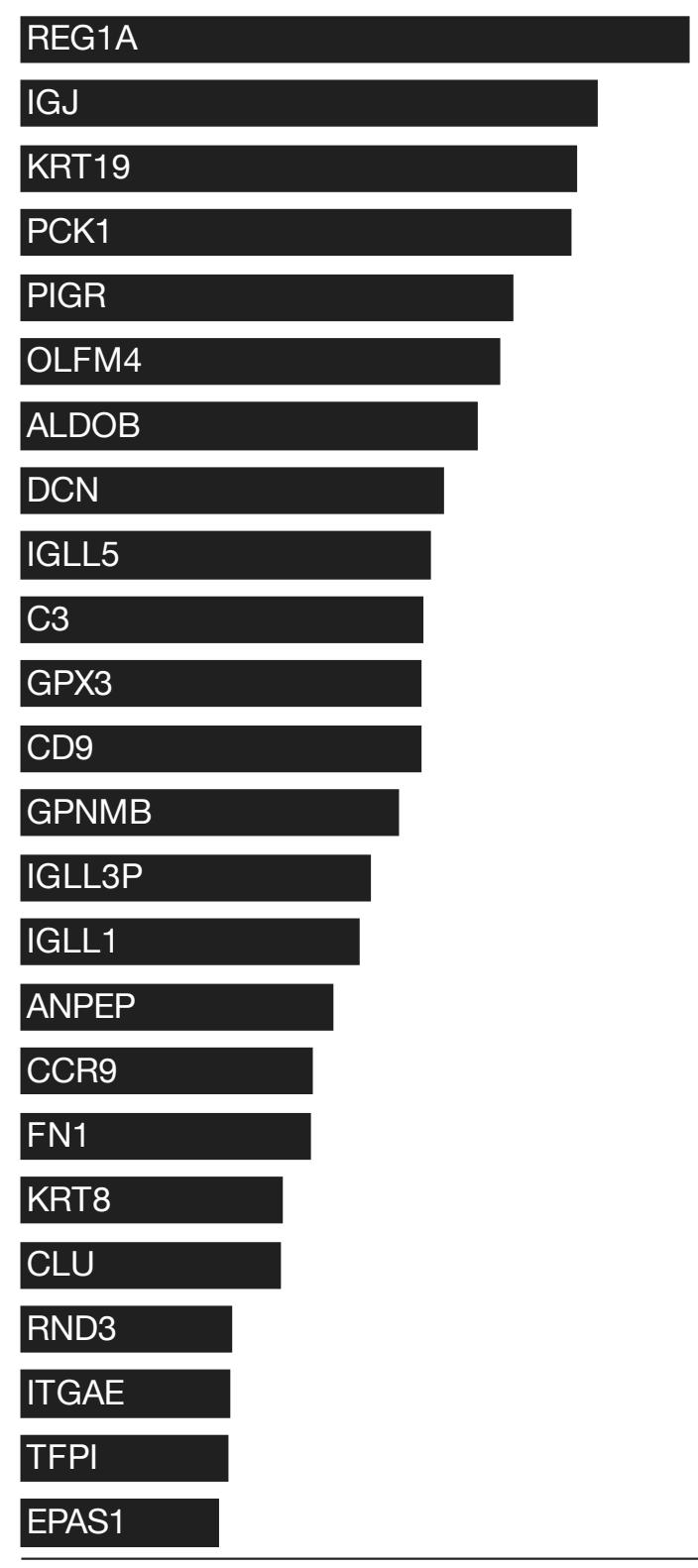


Figure S6

Figure S6: Significant differentially expressed genes between ILC subsets in spleen versus jejunum, Related to Figure 5

Bar plots depict mean \log_2 fold change of top genes significantly ($q<0.1$, $p<0.001$) enriched among all ILC and cNK subsets in A. spleen or B. jejunum. Data compiled from LP Jejunum ($n=5$), and Spleen ($n=5$) of 5 individuals. See also Table S5 for tissue- and subset-specific signature genes, Table S1 for donor information, and Table S6 for a summary of donors and tissues used per figure panel.

Donor #	Age	Sex	COD	HLA	CMV	EBV	Height (cm)	Weight (kg)	BMI	Donor count	44
					-	+				Male	30
					-	+	183	95	28.37	Female	14
40	30	M	A	A1, A66, B8, B35, DR16, DR17, DQ2, DQ5	-	+	178	88	27.77	Average	46.43
83	41	M	CS	A2, B7, B44, DR11, DQ7	-	+	183	95	28.37	Median	49.00
84	31	F	A	A1, A2, B35, B44, DR13, DR15, DQ6, DQ7	-	+	168	53	18.78	SD	14.44
89	59	F	A	A25, A30, B7, B37, DR11, DR15, DQ6, DQ7	-	+	170	90	31.14	Minimum	2.00
94	44	M	A	A33, A66, B65, B52, DR1, DR4, DQ5, DQ8	-	+	178	75	23.67	Maximum	70.00
95	60	M	A	02:02 33:01:01 53:01:01 42:01:01 03:01:01 03:02:01	+	+	190	91	25.21	Anoxia	27.27
108	53	M	CS	A24, A31, B27, B41, DR1, DR15, DQ5, DQ6	+	+	178	181	57.13	Head Trauma	20.45
110	40	F	CS	A30, A74, B44, B42, DRB13, DRB07	+	+	170	82	28.37	Stroke	50.00
124	26	M	HT	A23, A30, B57, B58, DR4, DR11, DR52, DR53, DQ7, DQ8	+	+	190	77.1	21.36	Other	2.27
134	28	M	HT	A11, A24, B35, B39, DR7, DR16, DR51, DR53, DQ2, DQ5	-	+	178	75	23.67	Average	29.16
138	35	M	A	A1, A33, B37, B65, DR1, DR11, DR52, DQ5, DQ7	+	+	165	90.7	33.31	Median	27.36
141	63	M	HT	A26, B35, DR4, DR53, DQ8	+	+	175	100.4	32.78	SD	8.99
150	39	M	CS	A24, A33, B35, B65, DR17, DR52, DQ2	+	+	177	86	27.45	Minimum	15.70
157	55	F	A	A2/30, B7/35, BW4, BW6, CW4/7, DR7/9, DR51-, DR52-, DR53-, DQ2	+	-	160	72	28.13	Maximum	59.33
159	57	F	A	A2/25, B18/27, BW4, BW6, CW2/12, DR1/15, DR51, DQ5/6	+	+	163	61	22.96	Negative	20
166	48	F	CS	A33/80, B35/42, BW6, CW4/17, DR11/18, DR52, DQ4/7	+	+	163	64	24.09	Positive	24
168	56	F	CS	A23/33, B53/75, BW4, Bw6, CW4, DR13/15, DR51, DR52, DQ6/9	-	+	168	137	48.54	Negative	4
169	33	M	HT	A3/24, B4/63, BW4+, BW6+, CW2/5, DR4/13, DR52+ + DR53+ + DQ7	+	+	183	99.4	29.68	Positive	39
171	66	M	HT	A1/31 B8/51 BW4+ + BW6+ + CW7/15 DR1/17 DR52 DQ2/5	+	+	173	81.6	27.26		
172	49	M	A	A24/68, B7/51, BW4, BW6, CW7/15, DR13/15, DR51, DR52, DQ5/6	+	+	168	107	37.91		
177	52	F	CS	A2/3, B7/57, BW4, BW6, CW6/7, DR7/15, DR51, DR53, DQ6/9	-	+	163	64.1	24.13		
178	51	M	CS	A2/30, B52/63, BW6, CW14/16, DR4/18, DR52, DR53, DQ4/8	-	+	182	72	21.74		
179	51	M	CS	A29, B13/44, BW4, CW6/16, DR7/103, DR53, DQ2/5	-	+	173	69.8	23.32		
181	46	M	CS	A2/66, B49/53, BW4+, CW4/7, DR11/18, DR52+, DQ4/6	-	-	178	129	40.71		
182	46	M	CS	A33/74, B53/65, BW4, BW6, CW4/8, DR11/17, DR52, DQ2/6	-	+	178	68	21.46		
183	69	F	CS	03:01:01:01 24:13:01 51:01:01 07:02:01 14:04	+	+	157	70.6	28.64		
189	59	M	CS	30:01:01 33:01:01 58:01:01 15:10:01 13: ? 11:04:01	+	+	175	84.5	27.59		
190	69	F	CS	A30, A68, B42, B58, BW4, BW6, CW6, CW17, DR12, DR18, DR52, DQ4, DC	+	+	165	71	26.08		
191	29	M	CS	A1, A2, B8, B50, BW6, CW6, CW7, DR7, DR17, DR52, DR53, DQ2	+	+	173	94	31.41		
193	50	M	A	A24, A29, B45, B52, BW4, BW6, CW15, CW16, DR15, DR16, DR51, DR6, DF	-	+	173	81.6	27.26		
196	45	F	CS	A2, A23, B57, B72, BW4, BW6, CW2, CW18, DR13, DR52, DQ6	+	-	165	58.4	21.45		
197	70	F	O	A2, B7, B35, BW6, CW4, CW7, DR12, DR15, DR51, DR52, DQ6, DQ7	-	+	152	81.7	35.36		
199	50	M	CS	HLA A2/3, B18/56, BW6, CW7, DR1/4, DR53, DQ5/8	+	+	183	74	22.10		
200	55	M	CS	A2, B7/49, BW4, BW6, Cw7, DR10/13, DR52, DQ5/6	-	+	183	198.7	59.33		
201	21	M	HT	A2, A33, B7, B58, BW4, BW6, CW7, CW10, DR1, DR17, DR52, DQ2, DQ5	+	-	183	79	23.59		
202	50	M	CS	A3/33, B7/53, BW4, BW6, CW4/7, DR8/9, DR53, DQ2/7	-	+	175	122	39.84		
203	70	M	CS	N/A	-	+	175	87	28.41		
204	30	M	CS	A3, A66, B44, B58, BW4, CW4, CW6, DR1, DR13, DR52, DQ5, DQ6	+	+	175	62.6	20.44		
205	45	F	CS	A1, A30, B8, B50, BW6, CW6, CW7, DR1, DR13, DR52, DQ5, DQ6	+	+	165	73.9	27.14		
206	50	M	A	A1, A25, B7, B8, BW6, CW7, DR15, DR17, DR51, DR52, DQ6, DQ2	-	+	185	118	34.48		
210	37	M	HT	A2/24 B35/51 BW4 BW6 CW1/4 DR4 DR53 DQ4/8	+	+	165	74	27.18		
213	2	F	HT	A3, A24, B7, B37, BW4, BW6, CW6, CW7, DR10, DR15, DR51, DQ5, DQ6	-	N/A	91	13	15.70		
216	34	M	HT	A2, A30, B50, B52, BW4, BW6, CW6, CW16, DR13, DR17, DR52, DQ2, DQ7	+	+	173	70.4	23.52		
217	49	M	A	A68, B7, B42, CW7, CW17, DR14, DR18, DR44, DQ5	+	+	173	103	34.41		

Table S1. Descriptive statistics and information for individual donors analyzed, Related to Figure 1

M- male, F- female; A- anoxia, HT- head trauma, CS- cerebrovascular stroke, O- other; COD- cause of death; SD- standard deviation; HLA- human leukocyte antigen

Age vs. Frequency

Tissue	cNK			ILC1			ILC2			ILC3		
	R	P	n	R	P	n	R	P	n	R	P	n
Abd. Fat	0.2639	0.3419	15	-0.1957	0.4846	15	0.2991	0.2788	15	-0.3178	0.2484	15
Mes. Fat	0.3053	0.2885	14	-0.2212	0.4472	14	-0.2774	0.3369	14	-0.3894	0.1688	14
Spleen	-0.03709	0.8915	16	-0.2331	0.3849	16	0.049	0.857	16	-0.1217	0.6535	16
mLN	0.3354	0.3435	10	0.04268	0.9068	10	-0.4146	0.2335	10	-0.3781	0.2814	10
IdLN	0.2155	0.3903	18	0.03627	0.8864	18	0.03109	0.9025	18	-0.4757	0.046	18
Lung	0.4596	0.0635	17	-0.3064	0.2317	17	0.0383	0.884	17	-0.3978	0.1138	17
LP Colon	0.2841	0.269	17	0.04694	0.858	17	0.4694	0.0573	17	-0.5658	0.0179	17
LP Ileum	0.07162	0.7998	15	0.1576	0.5749	15	-0.08594	0.7607	15	-0.005372	0.9848	15
LP Jejunum	0.4755	0.0396	19	-0.3961	0.0932	19	-0.3661	0.1232	19	0.007238	0.9765	19
IEL Colon	-0.02209	0.9353	16	0.2268	0.3983	16	-0.2872	0.2808	16	-0.08837	0.7449	16
IEL Ileum	0.2669	0.3781	13	-0.3329	0.2664	13	0.2204	0.4694	13	-0.1678	0.5837	13
IEL Jejunum	-0.3737	0.2314	12	-0.01424	0.965	12	-0.5419	0.0687	12	-0.1495	0.6429	12
Tissue	ILC1+			ILC1-			ILC3+			ILC3-		
	R	P	n	R	P	n	R	P	n	R	P	n
Abd. Fat	-0.2083	0.4564	15	-0.07996	0.777	15	-0.167	0.552	15	-0.3459	0.2066	15
Mes. Fat	-0.1527	0.6024	14	-0.3499	0.22	14	-0.1517	0.6046	14	-0.7	0.0053	14
Spleen	-0.07848	0.7727	16	-0.3415	0.1955	16	-0.08902	0.743	16	-0.2171	0.4193	16
mLN	0	>0.9999	10	0.03049	0.9334	10	-0.09756	0.7886	10	-0.2866	0.4221	10
IdLN	0.01036	0.9674	18	0.1399	0.5798	18	-0.5161	0.0284	18	-0.4425	0.0659	18
Lung	-0.3002	0.2417	17	-0.2878	0.2626	17	0.3224	0.2069	17	-0.1626	0.5331	17
LP Colon	0.09512	0.7165	17	0.02841	0.9138	17	-0.5365	0.0264	17	-0.551	0.0219	17
LP Ileum	-0.1328	0.6371	15	0.0752	0.79	15	-0.3584	0.1896	15	-0.1253	0.6563	15
LP Jejunum	-0.3079	0.1997	19	-0.4323	0.0645	19	-0.04063	0.8688	19	0.0009047	0.9971	19
IEL Colon	0.137	0.613	16	0.2135	0.4271	16	-0.218	0.4174	16	0.07364	0.7864	16
IEL Ileum	-0.1791	0.5583	13	-0.2228	0.4643	13	0.1458	0.6346	13	0.02476	0.936	13
IEL Jejunum	-0.452	0.1401	12	-0.5308	0.0758	12	-0.4104	0.1851	12	0.1073	0.7272	13

BMI vs. Frequency

Tissue	cNK			ILC1			ILC2			ILC3		
	R	P	n	R	P	n	R	P	n	R	P	n
Abd. Fat	0.1591	0.2856	11	-0.2413	0.1932	11	-0.1094	0.3489	11	0.02145	0.4705	11
Mes. Fat	0.1473	0.3079	19	-0.1473	0.3079	19	-0.4645	0.0471	19	-0.1824	0.2661	19
Spleen	-0.03235	0.4542	13	-0.362	0.0841	13	-0.387	0.0693	13	-0.2324	0.1926	13
mLN	0.2121	0.2801	16	-0.3091	0.1935	16	-0.2606	0.2349	16	-0.1879	0.3037	16
IdLN	0.257	0.1517	10	-0.4489	0.0308	10	-0.3044	0.1097	10	-0.08153	0.3739	10
Lung	0.2426	0.1733	15	0.01225	0.483	15	-0.299	0.1215	15	-0.06127	0.4084	15
LP Colon	0.3897	0.0615	18	-0.2549	0.1611	18	-0.06863	0.3974	18	-0.2598	0.1564	18
LP Ileum	0.2214	0.2133	17	-0.2786	0.1569	17	0.04286	0.4414	17	-0.07143	0.4013	17
LP Jejunum	0.08772	0.3605	17	-0.1737	0.2385	17	0.05965	0.4042	17	0.2915	0.113	17
IEL Colon	0.005887	0.4914	15	-0.09713	0.3602	15	-0.2237	0.2025	15	0.04709	0.4314	15
IEL Ileum	-0.04677	0.4397	14	-0.06327	0.4186	14	0.3939	0.0914	14	-0.008253	0.4911	14
IEL Jejunum	-0.4	0.1125	16	0.01818	0.4837	16	-0.1618	0.3173	16	0	0.5053	16
Tissue	+ILC1			-ILC1			+ILC3			-ILC3		
	R	P	n	R	P	n	R	P	n	R	P	n
Abd. Fat	-0.2538	0.1792	11	-0.1485	0.2987	11	-0.1859	0.252	11	-0.07175	0.3997	11
Mes. Fat	-0.08132	0.3924	19	-0.2508	0.1935	19	-0.05501	0.4261	19	-0.1435	0.3123	19
Spleen	-0.2504	0.1748	13	-0.3709	0.0787	13	-0.2706	0.1549	13	-0.07701	0.3884	13
mLN	-0.3951	0.1292	16	-0.2242	0.2683	16	-0.2727	0.2241	16	-0.1394	0.3536	16
IdLN	-0.2652	0.1437	10	-0.3891	0.0553	10	-0.04644	0.4274	10	-0.1228	0.3137	10
Lung	0.1544	0.2765	15	-0.04167	0.438	15	-0.01225	0.483	15	-0.1263	0.3145	15
LP Colon	-0.2941	0.1255	18	-0.05392	0.4194	18	-0.2955	0.1239	18	-0.2598	0.1564	18
LP Ileum	-0.6919	0.0021	17	-0.175	0.266	17	-0.5237	0.0237	17	0.1	0.362	17
LP Jejunum	-0.2509	0.1501	17	-0.1965	0.2101	17	0.05529	0.4111	17	0.3059	0.1014	17
IEL Colon	0.07506	0.3912	15	-0.106	0.3481	15	-0.1354	0.3073	15	0.3355	0.102	15
IEL Ileum	-0.5647	0.0222	14	-0.2091	0.2465	14	-0.2118	0.242	14	0.3466	0.123	14
IEL Jejunum	-0.4	0.1125	16	-0.2	0.2777	16	-0.1618	0.3273	16	0.1264	0.3414	16

Table S3. Correlation of ILC subset frequency versus donor age and BMI for each tissue, Related to Figure 2

R- Spearman correlation coefficient, P-associated p-value, n-number of XY pairs; Abd. Fat- abdominal fat; LP- lamina propria; IEL- intraepithelial lymphocytes; Mes. Fat- mesenteric fat; IdLN- lung- draining lymph nodes; mLN- mesenteric lymph nodes; Significant correlations ($p < 0.05$) are indicated by pink shading.

Gene	Jejunum NK			Spleen NK			Jejunum ILC1			Spleen ILC1		
	Avg.	SD	n	Avg.	SD	n	Avg.	SD	n	Avg.	SD	n
SELL	6.40	9.87	15	58.19	50.41	15	4.44	6.74	12	104.91	90.48	13
CX3CR1	9.41	21.21	15	44.81	50.65	15	0.56	1.62	12	1.41	3.18	13
FCGR3A	104.56	128.79	15	426.95	320.19	15	7.78	9.32	12	37.66	30.09	13
S1PR5	12.59	17.45	15	183.20	78.17	15	3.58	5.02	12	18.62	19.98	13
FCGR3B	2.42	3.32	15	5.39	3.74	15	0.19	0.64	12	1.08	1.05	13
IL9	0.00	0.00	15	0.00	0.00	15	0.00	0.00	12	0.00	0.00	13
CXCR3	13.45	9.83	15	3.94	6.06	15	2.97	3.36	12	5.11	5.08	13
PRDM1	230.23	99.04	15	186.43	77.18	15	95.67	70.99	12	51.50	21.82	13
KLRAP1	8.35	9.43	15	12.79	23.19	15	6.34	10.28	12	3.94	4.96	13
PTGDR2	0.00	0.00	15	0.00	0.00	15	1.45	2.63	12	0.54	1.04	13
IFNG	60.50	60.15	15	89.01	60.14	15	5.87	10.65	12	28.58	31.44	13
IL3RA	0.74	1.93	15	1.81	2.75	15	1.64	3.54	12	0.60	1.34	13
IL2RB	139.76	89.51	15	254.09	89.09	15	58.58	42.60	12	88.92	50.97	13
KLRC1	72.52	61.22	15	197.80	92.88	15	31.54	38.47	12	150.57	80.90	13
NCAM1	66.55	29.41	15	95.41	55.11	15	15.36	11.48	12	60.77	43.78	13
IL15RA	8.78	8.26	15	3.93	4.92	15	2.73	2.74	12	3.85	3.18	13
IL12RB2	12.07	12.26	15	38.14	20.77	15	7.70	6.65	12	24.68	13.06	13
EOMES	12.52	13.99	15	51.27	21.70	15	3.81	6.15	12	18.95	16.43	13
ISG20	144.44	94.45	15	160.34	79.50	15	55.57	44.16	12	108.15	72.55	13
ITGAM	10.59	17.64	15	80.15	59.74	15	2.59	4.95	12	33.07	27.80	13
CCL4	255.03	234.81	15	723.07	492.58	15	53.57	68.38	12	303.81	327.06	13
KLRC2	39.42	41.46	15	43.56	31.40	15	16.98	19.26	12	29.88	18.43	13
TBX21	6.06	4.25	15	12.94	6.71	15	2.06	2.52	12	5.44	5.89	13
KLRC3	156.62	162.98	15	142.29	52.69	15	88.63	135.42	12	87.87	40.67	13
CCR5	24.29	20.04	15	13.66	16.97	15	5.75	6.04	12	5.89	5.59	13
IL10RA	151.37	47.13	15	102.12	32.72	15	94.58	62.18	12	67.36	34.59	13
S1PR1	10.23	13.18	15	18.20	14.60	15	6.51	7.88	12	12.01	11.67	13
IRF8	124.40	80.84	15	294.04	185.43	15	83.08	76.15	12	218.67	152.30	13
KLRK1	241.31	143.23	15	411.37	119.88	15	155.32	120.79	12	280.07	158.95	13
IL2RG	155.46	46.98	15	240.91	54.28	15	103.40	67.54	12	144.24	57.05	13
KLRG1	14.56	15.39	15	38.13	38.44	15	11.26	12.59	12	16.52	17.39	13
KLRC4	28.17	28.18	15	36.34	21.36	15	8.25	10.17	12	20.04	13.09	13
NOTCH1	16.68	11.59	15	24.27	13.89	15	11.87	7.70	12	19.95	11.65	13
IL21R	43.29	27.06	15	46.68	22.71	15	31.63	13.28	12	38.66	24.71	13
IL10RB	34.49	20.31	15	32.68	17.84	15	25.36	18.42	12	34.42	16.64	13
KLRF1	54.03	57.66	15	283.98	153.67	15	14.86	26.44	12	130.24	100.25	13
IL27RA	18.58	9.46	15	25.37	12.05	15	15.52	13.70	12	12.32	8.93	13
GATA3	28.76	20.33	15	41.38	11.59	15	22.35	16.33	12	26.69	13.81	13
CCL1	0.00	0.00	15	0.00	0.00	15	0.00	0.00	12	0.00	0.00	13
NCR1	14.58	9.87	15	30.52	18.54	15	11.35	9.13	12	17.64	13.76	13
ETS1	127.97	59.42	15	319.90	87.65	15	100.80	53.70	12	160.02	63.34	13
KLRD1	400.39	164.47	15	798.05	200.78	15	328.45	228.80	12	484.44	191.94	13
TNFSF10	19.72	10.72	15	23.05	14.86	15	11.49	8.82	12	25.25	16.21	13
CXCR6	58.72	56.51	15	104.52	58.44	15	72.28	77.06	12	51.18	42.47	13
CD226	9.17	10.20	15	14.92	11.92	15	7.67	7.16	12	11.62	9.43	13
IFNAR2	30.31	19.02	15	38.24	17.76	15	25.39	18.77	12	20.27	14.50	13
KLF12	71.48	42.30	15	72.19	33.52	15	61.40	39.50	12	60.43	20.26	13
ZEB2	136.16	81.66	15	275.46	99.16	15	117.68	66.35	12	144.21	70.75	13
CXCR4	2261.03	1512.13	15	3093.39	1108.38	15	2021.07	1801.50	12	2977.74	1090.30	13
MAFF	22.44	14.76	15	30.56	17.60	15	20.16	15.15	12	19.67	9.85	13
BCL11B	9.93	9.62	15	11.26	9.41	15	8.99	8.13	12	6.15	5.00	13
TOX	59.50	46.43	15	71.26	32.35	15	56.85	50.23	12	50.43	41.03	13
IL2RA	19.36	13.86	15	19.57	20.77	15	58.85	28.82	12	43.46	38.54	13
NFIL3	28.04	12.92	15	41.43	21.02	15	29.59	17.01	12	26.38	10.61	13
RBPJ	65.57	24.40	15	36.93	12.79	15	76.38	25.90	12	84.65	43.33	13
ZBTB16	139.61	106.25	15	174.65	76.62	15	160.38	97.24	12	149.31	68.44	13
GF11	5.71	6.37	15	10.99	7.41	15	6.57	6.80	12	7.03	6.88	13
IFNGR2	17.26	15.83	15	3.90	7.40	15	6.19	4.52	12	9.18	11.71	13
IFNGR1	172.91	170.17	15	228.60	134.04	15	208.54	219.29	12	252.82	84.00	13
KLRB1	232.53	100.86	15	744.02	315.90	15	284.94	211.39	12	445.54	275.07	13
CSF2	0.15	0.42	15	0.50	1.09	15	0.79	1.69	12	2.44	3.59	13
IL17RA	16.60	8.65	15	18.60	8.75	15	44.61	53.64	12	20.53	17.12	13
STAT1	46.20	18.41	15	60.91	33.85	15	64.33	38.14	12	42.82	28.60	13
IL1RL1	3.07	7.18	15	2.44	2.49	15	4.37	6.53	12	4.32	4.31	13
AHR	65.46	20.94	15	37.91	27.78	15	97.09	20.50	12	62.13	18.18	13
IL4R	14.23	8.97	15	24.81	12.32	15	24.64	14.75	12	30.86	25.92	13
MCAM	13.42	10.43	15	32.95	35.39	15	29.57	17.90	12	30.05	17.53	13
IL2	1.75	2.60	15	0.18	0.40	15	4.84	6.25	12	1.07	2.57	13
IL18R1	21.70	19.96	15	49.71	28.69	15	49.95	38.98	12	68.94	41.59	13
RORC	1.85	5.80	15	0.80	2.36	15	4.35	5.90	12	4.93	5.43	13
CCL5	836.06	314.79	15	611.22	176.82	15	1078.22	1171.79	12	386.27	141.51	13
ITGA2	2.89	3.76	15	2.73	2.34	15	12.41	12.90	12	4.00	3.37	13
NCR2	8.96	15.71	15	0.06	0.23	15	9.42	14.44	12	0.59	1.08	13
KIT	7.70	13.76	15	3.00	4.52	15	120.06	141.37	12	58.87	74.29	13
ITGAE	163.73	199.45	15	23.35	11.35	15	135.68	165.67	12	21.58	11.08	13
IL7R	96.16	101.67	15	96.07	80.33	15	1689.40	1231.19	12	2436.51	925.74	13
KLRG2	0.00	0.00	15	0.00	0.00	15	0.00	0.00	12	0.00	0.00	13
KLRF2	3.33	6.02	15	0.03	0.11	15	3.70	4.35	12	3.48	4.16	13

Table S4. Select differentially expressed gene counts between jejunum- and spleen-localized cNK and ILC1, Related to Figure 5

Avg. – Average log normalized counts, SD – standard deviation, n – number of samples

ILC2 vs. ILC1	ILC2 vs. ILC3	ILC2 vs. NK	ILC2 vs. all	ILC3 vs. ILC1	ILC3 vs. ILC2	ILC3 vs. NK	ILC3 vs. all	ILC1 vs. NK
FPR1	CAMP	FPR1	HLA-DPB1	SVIL	PCDH9	TNS3	PCDH9	ICOS
FCN1	HLA-DPB1	CAMP	SERPINA1	TNS3	SLC4A10	CA2	AQP3	LTB
S100A9	ALPL	RETN	PLAUR	IL411	CLIC5	CLIC5	CA2	SLC4A10
THBS1	CR1	AGPAT9	FCN1	AQP3	CITED2	DLL1	SVIL	IL7R
PLAUR	IL10RA	EMR2	FPR1	SLC31A2	SPRY1	MBOAT7	IL411	DP4
SERPINA1	IL17RB	FXYD6	S100A9	TMED8	NCALD	CAT	SLC4A10	TNFRSF25
PDE2A	SAPCD2	PTGS2	THBS1	CYP26A1	HOXA7	IZUMO4	IL1R1	CA2
CFP	SH3BP5	LRRK2	ANPEP	MYB	RORC	EPHB3	IL7R	DP4
PLBD1	TBC1D9	CIITA	CLU	ARHGAP32	PLCB4	TOM1L1	ICOS	IL7R
NCF2	TRPM2	CD33	ALDH1A1	SCHIP1	SPTLC3	PARD3B	TNFRSF25	LTB
EMR1		MS4A6A	HLA-DRA	SEMA6C	FAM189A2	CYP2E1	KIT	TNFRSF25
MMP19		IL3RA	CD74	SLCO2A1	TNFRSF11A	COL4A3	GPR133	SLC4A10
SOD2		HLA-DRB5	IL1B	KDR	TEX30	KIAA1324	AMICA1	CA2
S100A6		ICOS	IL1R2	RASD1	LDLRAD3	ABC5	RUNX2	ICOS
TIMP1		PTGDR2	ACSL1	TOB1	DHRS3	SORCS1	KLF4	BCL11A
KCTD12			IFI30	TNFSF11	CD2	APP	MMRN1	CD1C
PILRA			CD14	HPN	TNFSF4	CTDSPL		BACE2
FCGR1A			C5AR1		TOX2	HHAT		TLR10
ADAMTS2			S100A8		ZNF618	SAMD4A		IAPP
LILRA3			VCAN		RCAN2	PRR5		MPV17L
IL1RL1			LYZ		SPINK2	RNF144A		ABC5
CAV1					KIAA0087	DOCK5		PCDH9
FCGR1					SPEF2	FAM134B		EVA1C
LILRB4					PPP1R9A	SOGA2		IL23R
IL3RA						AFAP1L1		RFX2
						VWA5A		CD40LG
						FGD6		

Table S5. Genes significantly enriched in ILC2 (blue), ILC3 (green), and ILC1 (red) versus other subsets across all tissues, Related to Figure 5 and Figure 6

Highlighted "signature" genes are significantly enriched in the indicated subset compared to multiple other ILC subsets.

Fig.	Panel	Donors (N)	Tissue(s)	Samples (n)	Fig.	Panel	Donors (N)	Tissue(s)	Samples (n)
1	B-D	44	-	-	4	A-C	5	Jejunum	5
	E	1	-	1				Lung	5
2	A	44	Abd. Fat	11				Spleen	5
			IEL Colon	15	5	A-E	5	Jejunum	5
			IEL Ileum	14				Spleen	5
			IEL Jejunum	16	6	A-E	5	Jejunum	5
			IdLN	10				Spleen	5
			LP Colon	18	S1	A-C	1	Blood	1
			LP Ileum	17				Colon	1
			LP Jejunum	17				Lung	1
			Lung	15		D-F	1	LLN	1
			Mes. Fat	19				Jejunum	1
			mLN	16				Blood	1
			Spleen	13				Ileum	1
	B-C	1	-	1				Lung	1
	D	44	Abd. Fat	11	S2	B	1	SI IEL	1
			IEL Colon	15		C-E	11	Lung	11
			IEL Ileum	14				LdLN	8
			IEL Jejunum	16				IWAT	7
			IdLN	10				EWAT	7
			LP Colon	18				MWAT	7
			LP Ileum	17				MLN	7
			LP Jejunum	17				Spleen	4
			Lung	15				Colon LP	3
			Mes. Fat	19				Colon IEL	4
			mLN	16				SI IEL	7
			Spleen	13	S3	C	44	Abd. Fat	11
	E-F	44	Abd. Fat	11				IEL Colon	15
			IEL Colon	15		F		IEL Ileum	14
			IEL Ileum	14				IEL Jejunum	16
			IEL Jejunum	16				IdLN	10
			IdLN	10		B		LP Colon	18
			LP Colon	18				LP Ileum	17
			LP Ileum	17		D		LP Jejunum	17
			LP Jejunum	17		A		Lung	15
			Lung	15		E		Mes. Fat	19
			Mes. Fat	19				mLN	16
			mLN	16				Spleen	13
			Spleen	13	G-H	1	-	-	1
3	A-D	44	Abd. Fat	11	S4	A-C	5	Jejunum	5
			IEL Colon	15				Lung	5
			IEL Ileum	14				Spleen	5
			IEL Jejunum	16	S5	A-C	5	Jejunum	5
			IdLN	10				Lung	5
			LP Colon	18				Spleen	5
			LP Ileum	17	S6	A-B	5	Jejunum	5
			LP Jejunum	17				Spleen	5
			Lung	15					
			Mes. Fat	19					
			mLN	16					
			Spleen	13					
	E-F	44	Abd. Fat	11					
			IEL Colon	15					
			IEL Ileum	14					
			IEL Jejunum	16					
			IdLN	10					
			LP Colon	18					
			LP Ileum	17					
			LP Jejunum	17					
			Lung	15					
			Mes. Fat	19					
			mLN	16					
			Spleen	13					

Table S6. Summary of all donors, tissues, and samples analyzed per figure for all figures and panels, Related to Figures 1-6, Figures S1-S6

Abd. Fat- abdominal fat; LP- lamina propria; IEL- intraepithelial lymphocytes; Mes. Fat- mesenteric fat; IdLN- lung- draining lymph nodes; mLNs- mesenteric lymph nodes;